The emerging osteo-metabolic phenotype of COVID-19: clinical and pathophysiological aspects

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An emerging feature of COVID-19 is a clinically relevant osteo-metabolic phenotype characterized by widespread acute hypocalcaemia and chronic hypovitaminosis D with high prevalence of vertebral fractures. This phenotype might have negative effects on disease severity and its components could represent possible targets for prevention of SARS-CoV-2 infection and poor COVID-19 outcomes.

The clinical course of coronavirus disease 2019 (COVID-19; caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) is mainly characterized by respiratory features and can range from asymptomatic or mild disease to severe forms with a high risk of death[1]. During the spread of the pandemic, several studies have shown that the endocrine and metabolic features of COVID-19 were strongly relevant clinical manifestations[1]. Some papers have now highlighted an emerging osteo-metabolic phenotype of COVID-19, which might influence COVID-19 severity and clinical outcomes. This phenotype is typically characterized by widespread acute hypocalcaemia and chronic hypovitaminosis D, as well as a high prevalence of morphometric vertebral fractures[2–4].

The initial reports of clinical and laboratory characteristics of patients with COVID-19 did not include population data on mineral metabolism. In April 2020, a case of severe acute hypocalcaemia in an Italian patient with SARS-CoV-2 infection who had previously undergone thyroidectomy was reported. This report suggested that COVID-19 was a possible precipitating cause of subclinical post-surgical hypoparathyroidism[5]. Interestingly, previous reports on patients with SARS and Ebola virus infection had described hypocalcaemia as a highly prevalent biochemical abnormality, ranging from 60% of patients at hospital admission to 75% during hospitalization[2].

Following the first reported case of acute hypocalcaemia in a patient with COVID-19, several studies worldwide showed a very high prevalence of hypocalcaemia in hospitalized patients with COVID-19, ranging from 62.6% to 87.2%, depending on the definition criteria[2]. Furthermore, low calcium levels were associated with worse disease outcomes, increased levels of markers for biochemical inflammation and thrombosis (such as C-reactive protein, lactate dehydrogenase, IL-6 and D-dimer) and an increased risk of in-hospital short-term and 28-day mortality[2]. Hypocalcaemia, detected at first evaluation on admission to an emergency department for COVID-19, was also identified as a significant independent risk factor for hospitalization[6].

Several pathophysiological mechanisms have been investigated to clarify COVID-19-related hypocalcaemia. These mechanisms include increased calcium depletion due to the calcium-dependent mechanisms of action of the virus, acute malnutrition during critical illness, the role of calcium ions in coagulation and prothrombotic status, high levels of unbound and unsaturated fatty acids in the inflammatory response and hypovitaminosis D[2]. In addition, as hypocalcaemia also seems to be a distinctive biochemical feature of COVID-19 (REF.[7]), calcium levels might be a useful laboratory marker of disease aggressiveness as well as a potential therapeutic target that can be easily evaluated in emergency referrals.

At the beginning of the COVID-19 spread in Europe, vitamin D deficiency was hypothesized to have a role in increased SARS-CoV-2 infection susceptibility and negative outcomes of COVID-19 (REF.[3]). In fact, vitamin D is well known to be crucial for skeletal homeostasis, but it also has many extra-skeletal systemic functions, including immunomodulation and immunocompetence in innate and adaptive immunity[8]. This original hypothesis was based on the immunomodulatory role of vitamin D and the widespread vitamin D deficiency in areas heavily affected by the pandemic, such as Italy and Spain. The hypothesis is consistent with several findings showing low levels of vitamin D in hospitalized patients with COVID-19 and with reported correlations between vitamin D levels and clinical severity patterns and outcomes[8]. Furthermore, vitamin D deficiency is also very frequent in patients with type 2 diabetes mellitus and obesity who are known to be at increased risk of severe COVID-19 (REF.[3]).

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In patients with obesity, low levels of vitamin D are inversely related to BMI and adiposity, negatively influencing skeletal and muscle health with a resulting increased predisposition to an obese osteo-sarcopenic phenotype[3]. As vitamin D can also have a protective effect on β-cells and might modulate adipose tissue distribution[3], it can be hypothesized that a bidirectional relationship exists between diabetes mellitus, altered body composition and reduced vitamin D levels. This relationship might have clinical implications in patients with COVID-19, increasing their risk of poor outcomes[3].

Based on these findings, a possible protective role of vitamin D treatment in patients with COVID-19 was suggested but, to date, only a few peer-reviewed observational studies and small randomized open-label clinical trials of uncertain quality have been performed, and they had conflicting results. However, it is conceivable that effectively tackling hypovitaminosis D in populations at high risk of COVID-19 (for example, patients who are older, have diabetes mellitus or have obesity) might have an important role in reducing the risk of COVID-19, as well as other acute respiratory infections[9].

In addition, hospitalized patients with COVID-19 are characterized by the presence of multiple predisposing factors for bone frailty with a high risk of fractures. In fact, besides a high rate of hypocalcaemia, widespread hypovitaminosis D and older age, these patients are often affected by several comorbidities known to increase secondary osteoporosis risk, such as type 2 diabetes mellitus and cardiovascular diseases[4]. Vertebral fractures are one of the most frequent osteoporotic fracture types, decreasing survival and impairing quality of life in the general population. Previous studies showed that vertebral fractures negatively influence respiratory function, decreasing pulmonary vital capacity, and they might lead to a restrictive pulmonary dysfunction and increase the risk of pneumonia in patients without previous pulmonary diseases[4].

The relationship between mortality, impaired respiratory function and increased pneumonia risk in patients with vertebral fractures prompted us to investigate vertebral fracture prevalence and influence on clinical outcomes in patients with COVID-19 using lateral chest X-rays performed at admission in the emergency department[4]. In this cohort, 36% had at least one thoracic vertebral fracture. Interestingly, patients with a morphometric fracture more frequently required noninvasive mechanical ventilation and their mortality rate was almost doubled compared with patients who did not have a fracture[4]. Owing to the negative effect of vertebral fractures on respiratory function and survival, vertebral fracture evaluation on chest X-rays might be a useful and easy-to-perform assessment to predict a patient's frailty and poor general health. Furthermore, as anti-osteoporotic treatments do not seem to cause an increased predisposition to COVID-19 (although this can also be explained by their association with vitamin D supplementation)[10], they should be continued during the pandemic to avoid an increased fracture risk, which might be detrimental in the context of COVID-19.

In conclusion, within the endocrine and metabolic comorbidities reported in patients with COVID-19 (REF.[1]), a distinct osteo-metabolic phenotype can be observed. This phenotype is characterized by a high rate of acute hypocalcaemia in the context of widespread chronic hypovitaminosis D and high prevalence of vertebral fractures. In our study population, vertebral fractures seem to be one of the most common comorbidities of COVID-19. This emerging phenotype is potentially clinically relevant in patients with COVID-19, owing to the negative relationship of all its components with SARS-CoV-2 infection severity.

Finally, owing to the prognostic relevance of this osteo-metabolic phenotype, its components might be suitable targets for laboratory and radiological assessment, as well as possible targets to prevent SARS-CoV-2 infection and poor COVID-19 outcomes. For instance, vitamin D replacement in the general population (particularly in high risk patients with vitamin D deficiency) and avoiding discontinuation of anti-osteoporotic treatment. Calcium supplements should be considered in patients with acute hypocalcaemia admitted to hospital with COVID-19, particularly in those with severe hypocalcaemia owing to its potentially harmful effects on the cardiac and central nervous systems[2].

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Competing interests
The authors declare no competing interests.